Staging and treatment related problems of loco-regional disease in patients with esophageal cancer

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CHAPTER 7

Impact of splenectomy on surgical outcome in patients with cancer of the distal esophagus and gastro-esophageal junction

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Introduction

Tumors at or near the gastroesophageal junction are usually in an advanced stage with a dismal prognosis at the time of surgery. Potentially curative treatment exists of a radical complete resection of the primary tumor en bloc with distal mediastinal and abdominal D2 lymph node dissection around the celiac trunc. For adequate nodal clearance splenectomy has been performed as a part of the planned radical procedure.

In gastric cancer large randomized European trials failed to demonstrate a survival benefit for radical D2 resections, including extended lymphadenectomy of the first and second lymph node regions with splenectomy.[1-3] D2 nodal dissections were associated with a relatively high morbidity and in-hospital mortality and long hospital stay.[1;4;5] Whether splenectomy has a negative impact is debatable as these results are in contrast with those from several studies in Japan, where D2 resections are performed routinely[6-9].

In contrast to splenectomy in gastric cancer, available data regarding clinical outcome in patients with splenectomy during resection of distal esophageal or gastro-esophageal junction (GEJ) tumors are scarce. The purpose of this study was to determine whether intentional splenectomy during resection of tumors near or at the GE junction is associated with higher morbidity and in-hospital mortality and decreased cancer survival.

Patients and methods

Patients characteristics and treatment

Between January 1991 and July 2004, 210 patients with cancer of the distal esophagus or GEJ underwent esophagectomy with curative intent. Since January 1991 we collected data concerning treatment and follow up in a database. All patients had given consent and after approval by the Institutional Ethic Committee, all data were analyzed retrospectively for surgical evaluation and outcome. Most tumors were adenocarcinomas (85.2%) and were located at the distal esophagus and GEJ (53% and 40%, respectively). Splenectomy was performed in 66 patients (Group I) and was not performed in 144 patients (Group II). Patients' characteristics are summarized in table 1. All patients were treated by the same surgical group and underwent a standard curative intended resection, either a distal esophagus/cardia resection by a left thoraco-mid laparotomy with cervical anastomosis or a subtotal esophageal resection (right thoraco-mid laparotomy with cervical anastomosis). Both were combined with a two-field lymphadenectomy (D2) of nodes at the celiac trunk, upper borders of the pancreas, para-aortic region and the mediastinal nodes. On forehand interrelatedness and possible confounding factors for outcome of surgical techniques were calculated and were not found to be interfering with prognosis or survival. All splenectomies were performed on oncological reasons, for better clearance of suspicious lymph nodes along the splenic artery or near the splenic hilum and for tumors located near or at the GEJ or those with extended

growth along the greater curvature of the proximal stomach. The extent of gastric resection was more extensive in group I as was the extent of esophageal resection in Group II. Blood transfusion was measured during operation and for the early postoperative period of 4 weeks. Tumor stage and grade were classified according to the sixth edition of the tumor-node-metastasis system classification and the residual tumor (R) classification of the International Union Against Cancer and the American Joint Committee on Cancer.[10;11] None of the patients received neoadjuvant treatment.

Postoperative complications

Major complications were categorized in serious infectious complications (systemic inflammatory response syndrome (SIRS), sepsis, anastomotic leakage considered as anastomotic insufficiency requiring surgical intervention intra-abdominal abscess requiring drainage, deep wound infections and pulmonary infections, including pneumonia with positive bacteria culture of sputum and non-infectious complications, including atelectases, postoperative bleeding, chylothorax, thrombo-embolism, other pulmonary complications and cardiac complications.[12] Regarding the occurrence of these complications we reviewed the impact of splenectomy on morbidity and mortality, hospital stay, operation room (OR) time, Intensive care (IC) stay, and the administration of red blood cells (RBC).

Follow-up

All medical data was collected prospectively in a patient research database. Patients were seen in the outpatient department every 3 months for the first postoperative year, every 6 months for the next year and then annually for ten years.

Relevant information was collected from the medical records, general practitioners, the research database and the Comprehensive Cancer Center North Netherlands to determine patient demographics, tumor characteristics, treatment related factors, postoperative course (morbidity, mortality and hospital course) and long term follow-up.

Statistical analyses

To avoid possible confounding factors between the two groups, preliminary univariate analyses were performed to select factors for the multivariable Cox Regression analysis. Factors with a p-value > 0.1 were not selected. Covariance of these selected factors was explored. Possible interrelatedness of surgical variables was calculated with a cross-tab and Chi square.

Mortality included all in-hospital deaths within the same hospital admission or any death within 30 days of operation. Follow-up was calculated from the time of surgery until death (survival time) at a minimum follow-up of two years. Data was reflected as medians with percentages. Continuous variables were significantly compared by using the T-test and the Chi-Square test. Survival rates calculated by the Kaplan-Meier method and the log rank test were used for comparison of the survival curves. The Mann-Whitney test was performed to calculate and compare the significance

of hospital periods in the different groups. Prognostic factors were calculated with Cox regression univariate and multivariate analyzes. All possible interfering factors for survival in the database were included in the univariate analysis. Multivariate Cox regression was performed by incorporating factors as covariates with a p-value ≤ 0.1 on univariate analysis.

A p-value <0.05 was considered to be significant. Statistical computations and figuring were all performed by using the statistical package SPSS version 12.02 (SPSS Inc., Chicago, IL).

Results

General

Almost 40% of all tumors were in stage III and nodal metastases were detected in 54.8% and equally distributed between both groups (Table 1). Gender and age at surgery did not differ between both groups. Adenocarcinoma was the main histological type; 95.5% and 80.6% in group I and II, respectively. In group I most tumors were Siewert type II lesions located at the GEJ (71.2%), while those in group II were predominately type I lesions located in the distal esophagus (74.3%). Type III lesions were not included in this study as they were considered as belonging to gastric tumors.

Table 1. Patient characteristics: Distribution of clinicopathological and treatment related factors in the splenectomy group (I) and the non-splenectomy group (II).

	Group I	Group II	P value
Total number (%)	66 (31.4)	144 (68.6)	-
Gender (%)			
Male	55 (83.3)	112 (77.8)	0.355
Female	11 (16.7)	32 (22.2)	
Age (yrs)			
Median	62.8	64.3	0.895
Range	(36.1 – 79.5)	(29.1 – 83.0)	
Localization (%)			
Distal esophagus	19 (28.8)	107 (74.3)	<0.001 *
GEJ	47 (71.2)	37 (25.7)	
Histology (%)			
Adenocarcinoma	63 (95.5)	116 (80.6)	0.011 *
Squamous cell carcinoma	3 (4.5)	25 (17.4)	
Others	0 (0)	3 (1.4)	
Type of anastomosis			
Cervical	2 (3.0)	74 (51.4)	<0.001 *
Intrathoracic	64 (97.0)	70 (48.6)	
Tumor stage (%)			
I	5 (7.6)	28 (19.4)	0.066
IIa	22 (33.3)	32 (22.2)	
IIb	6 (9.1)	18 (12.5)	
III	27 (40.9)	57 (39.6)	
IV	6 (9.1)	9 (6.3)	

Median follow-up was 16 months (range 1-159 months) and no patient was lost during the follow-up.

Surgery

Surgical variables, including the surgical procedure (p=0.464), tumor location (p=0.153), histology (p=0.372) and type of anastomosis (p=0.645)) were explored statistically for an adequate evaluation between both groups without confounding factors. As expected there was a significant mutual interrelatedness between surgical procedure, localization, histology and type of anastomosis. Because none of these variables were of any prognostic value in univariate analyses, this interrelatedness was not problematic for further evaluation of the two groups.

Table 2. Postoperative complications in the splenectomy group (I) and the non-splenectomy group (II).

	Group I	Group II	P value
Radicality of surgery (%)			
R0	59 (89.4)	125 (86.6)	0.467
R1	7 (10.6)	17 (11.8)	
R2	0 (0)	2 (1.4)	
Mortality (%)			
	6 (9.1)	5 (3.5)	0.721
Morbidity			
Major infectious complications (%)	18 (27.4)	32 (48.5)	NS
SIRS	0 (0)	4 (2.8)	0.173
Sepsis	8 (12.1)	17 (9.7)	0.948
Anastomotic leakage	9 (13.6)	23 (16.0)	0.663
Intra-abdominal abcess	2 (3.0)	1 (0.7)	0.186
Severe wound infection	2 (3.0)	8 (5.6)	0.426
Pulmonary infection	5 (7.6)	18 (12.5)	0.290
Major non-infectious complications (%)	48 (33.3)	80 955.6)	NS
Atelectasis	6 (9.1)	13 (9.0)	0.988
Postop. Bleeding	0 (0)	6 (4.2)	0.093
Chylothorax	0 (0)	7 (4.9)	0.069
Thrombo-Embolism	2 (3.0)	1 (0.7)	0.186
Wound dehiscence	0 (0)	4 (2.8)	0.173
Pulmonary complications	26 (39.4)	53 (36.8)	0.720
Cardiac complications	12 (18.2)	25 (17.4)	0.885
Hospital stay			
median (range) days	23 (10-89)	22 (7-102)	0.513
OR Time			
median (range) hours	6.4 (3.4-10.2)	4.9 (3-7)	<0.001
IC stay			
median (range) days	3.0 (0-64.0)	1.0 (0-47)	0.010
RBC's administered			
median (range) units	2.0 (0-10)	0.0 (0-41)	<0.001

Microscopically radical resections (R0) were equally performed in both groups: 59 patients (89.4%) in group I and 125 (86.6%) in group II. There was no difference in the radicality of surgery between both groups (p=0.467) (Table 2).

Postoperative course

The overall postoperative mortality rate was 5.2% and did not differ between the groups (Table 2). Postoperative complications occurred in 27 patients in group I (40.9%) and in 68 patients in group II (47.2%), without any difference between both groups (p=0.4). In group I, 18 (27.3%) patients had serious infectious complications and 32 (48.5%) patients noninfectious complications compared to 48 (33.3%) and 80 (55.6%) patients in group II, respectively. Pulmonary complications were most frequently reported; 39% in group I and 37% in group II. Anastomotic leakage was the most common infectious complication with 13.6% in group I and 16.0% in group II. Hospital stay was not

Table 3. Prognostic factors of survival between both groups in univariate analysis.
* Significant p value (p< 0.10)

Factor		Hazard Ratio	95% CI		P value
			Lower	Upper	
Splenectomy					
No	Reference				
Yes		1.379	0.947	2.007	0.094 *
Radicality of surgery					
R0	Reference				
R1		2.499	1.656	3.770	<0.001 *
Nodal metastases					
N0	Reference				
N1		2.704	1.821	4.017	<0.001 *
Complications					
No	Reference				
Yes		1.696	1.163	2.473	0.006 *
Infectious compl.					
No	Reference				
Yes		1.544	1.041	2.292	0.031 *
Non-infectious compl.					
No	Reference				
Yes		1.360	0.929	1.992	0.113
Periods					
Hospital stay		1.010	1.000	1.020	0.041 *
OR Time		0.970	0.834	1.129	0.694
IC stay		1.032	1.016	1.048	<0.001 *
RBC's		1.407	0.958	2.068	0.082 *

different between both groups (p=0.5). However, there was an increased OR time (p=<0.001) with a prolonged IC stay in group I (p=0.01). There was also a higher administration of red blood cells (RBC's) during surgery and early postoperative period (< 4weeks) in group I (p=<0.001)

Survival

The one year survival for the whole group was 75% with an overall survival of 49.5% (1-150 months). A decrease in overall survival was observed in group I, although it was not significantly (p=0.09; Figure. I). However, the one- and two-year survival was significantly worse in patients with splenectomy, 69.7% and 56.1% for group I and 75% and 67.4% for group II (p=0.032 and p=0.017). An obvious but not significantly difference in long term 5-year survival was found, 28.8% in group I and 59.7% in group II (p=0.191; Figure I).

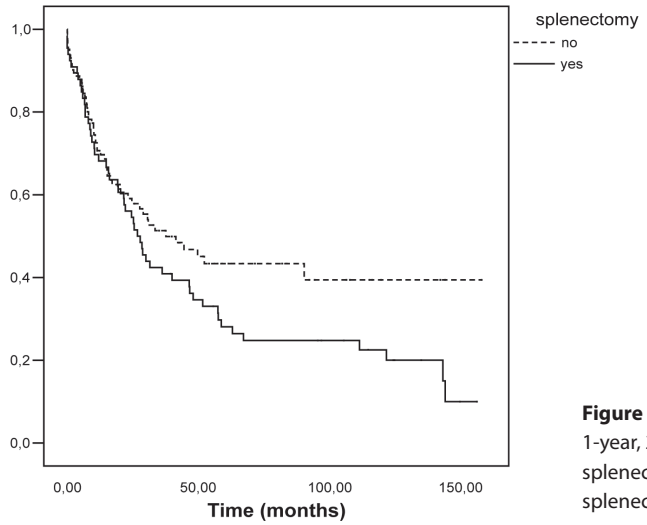

Figure I. Overall survival (p=0.092) and 1-year, 2-year and 5-year survival in the splenectomy group (I) and the non-splenectomy group (II).

Prognostic factors for survival

Splenectomy itself had no significant impact on survival (p=0.094). However, in both groups, positive lymph nodes (N1) had a significantly worse impact on survival (p<0.001). Radicality of surgery (R0) and occurrence of complications had a negative effect in both groups (respectively p<0.001 and p=0.006). Infectious complications were prognostic important (Table 3; p=0.03) and especially, sepsis (HR:4.389, CI: 2.597 and 7.417; p=<0.001) and anastomotic leakage (HR:2.345, CI 1.476 and 3.727; p=<0.001) had a significant negative effect on survival. Of the non-infectious complications, only pulmonary complications had a negative impact (HR: 1.546, CI 1.057 and 2.261; p=0.025). Other prognostic factors were hospital stay (p= 0.04), IC time (p<0.001) and RBC's administration (p=0.08) (Table 3).

Multivariate analysis showed that gender (p=0.03), surgical radicality (p<0.001), nodal metastases (p<0.001), overall complications (p=0.02) and IC stay (p=0.017) were significant independent factors on the survival of patients in group I compared to group II (Table 4).

Tabel 4. Independent prognostic factors of survival between both groups in multivariate analysis (Cox Regression). * Significant p value (p< 0.05)

Factor	Hazard Ratio	95% Confidential interval		P value
		Lower	Upper	
Gender	0.606	0.350	1.051	0.029 *
Radicality of surgery	2.323	1.524	3.541	<0.001 *
Nodal metastases	2.621	1.749	3.929	<0.001 *
Complications	1.737	1.087	2.775	0.021 *
Sepsis	3.441	1.856	6.381	<0.001 *
Anastomotic leakage	1.405	0.756	2.612	0.283
Pulmonary compl.	1.119	0.705	1.778	0.633
Hospital stay	0.992	0.976	1.008	0.325
ICU stay	1.030	1.005	1.055	0.017 *
RBC's administering	0.966	0.919	1.014	0.163

Discussion

In this study of esophageal cancers no difference was observed in mortality and morbidity after splenectomy during resection of distal esophagus and gastroesophageal tumors. Patients had a higher frequency of blood transfusions, prolonged ICU stay and OR time after splenectomy. Gender, radicality of surgery, complications, including sepsis and ICU stay were independent prognostic factors for survival. While splenectomy had no significant prognostic effect on overall survival, the 1- and 2-year survival was significantly decreased in the splenectomy group.

The extent of surgery in cancers around the gastro-esophageal (GE) junction, including Siewert type I within the distal esophagus and type II at the GE junction, is still controversial[13]. Lymph node dissection in these tumors usually includes removal of sub-aortic mediastinal and para-aortic nodes and those along the celiac trunk, hepatic artery and splenic artery.

in several studies splenectomy showed to have a negative impact on survival in patients with various gastrointestinal cancers, particularly in gastric and colon cancer.[1;3-5;14-21] Furthermore, anatomical studies revealed a low mean number of 2.2 to 3 lymph nodes in the splenic hilum. Moreover, splenic node metastases rarely occur in esophageal cancer and if present they are mainly observed in advanced stage IIIb and IV tumors.[22] Splenectomy alters the immune system with impairment of Kupffer cell response and long-term T-cell depression, leading to a diminished capacity in removing tumor micro metastases.[19;20] Furthermore, there is a significant reduction in circulating immunoglobulin M in the early postoperative period with an increased risk of overwhelming post-splenectomy sepsis.[1;2;4;23-26]

Splenectomy is often linked with elevated complications without improving survival rates.[5;27;28] In the Dutch and British gastric cancer trials extended dissection with splenectomy was an independent risk factor for surgical complications and associated with increased morbidity and mortality reducing the overall survival.[1;4;29] Other studies however, found no increase in hospital mortality in the splenectomy group.[22;23]

The occurrence of lymph node metastases in the splenic hilum is thought to be higher in proximal gastric and GEJ tumors.[22;30-32] Splenectomy is therefore frequently included as a part of a planned radical resection of adenocarcinoma in the proximal third of the stomach. Based on the high mortality rate in D2 resections in randomized studies in Europe many surgeons abandoned the splenectomy principle.

Griffith et al. described splenectomy as an independent predictor of poor outcome, in regard to death from recurrent cancer.[15] The spleen itself is seldom affected by cancer of the esophagus and GEJ, though the lymph nodes in the splenic hilum are sometimes affected. Splenectomy might therefore theoretically improve prognosis by achieving better lymph node clearance facilitating complete resection to obtain long-term control. The need for splenectomy in these patients as a part of the procedure in improving complete tumor removal is a difficult issue as data about incidence of nodal metastasis to the splenic hilum are scarce and controversial.

According to the literature application of blood transfusion demonstrated a worse prognosis independent of disease stage or the presence of major complications.[33;34] Some studies suggest an interaction of blood transfusion and splenectomy in their adversely effect on survival similar to the findings in the transplantation literature.[32] In patients with gastric cancer the adverse effect of allogeneic blood transfusion on prognosis seems to be associated with the presence of an intact spleen and is abrogated by its absence, which points toward an immunologic mechanism.[32;34] Dresner et al. also described a significantly worse prognosis after radical esophagectomies with a survival benefit by avoiding unnecessary transfusion.[33]

It is still debatable whether splenectomy is associated with an increased mortality regarding infectious complications.[35] However, patients with esophageal cancer are generally in a deteriorated condition leading to a substantial risk of infectious complications. In our study sepsis was linked with a lower survival rate. Avoidance of splenectomy and minimizing operation time and blood loss might therefore not only decrease postoperative infectious complications with additional mortality, but might lead to a better early survival in these patients

In gastric cancer preservation of the spleen is recommended as it seems to improve survival after radical surgery. During esophagectomy splenectomy is only justified in gastroesophageal tumors with extension close to the spleen or with obvious lymph node metastases at the splenic hilum. However, the spleen itself is seldom infiltrated by esophageal cancer and the existence of nodal metastases to the splenic hilum is rare. In absence of long term survival benefit in the splenectomy group we conclude that the spleen should be preserved in the course of a potentially curative resection of distal esophageal and GEJ tumors.

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